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5,5-Dimethylhydantoin (DMH) High Production Volume (HPV) Chemical Challenge

Test Plan

Prepared for:

American Chemistry Council
Brominated Biocides Panel
DMH Task Group

Prepared by:

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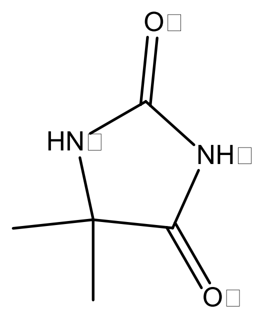
Identity

5,5-Dimethylhydantoin (DMH) is a chemical with the structure:



5,5-Dimethylhydantoin (CAS RN 77-71-4)

Chemical Formula: $C_5H_8N_2O_2$

Molecular Weight: 128.15

Color/Form: White, crystalline solid

Data Availability

5,5-Dimethylhydantoin is a precursor molecule used in the production of FIFRA registered halohydantoin biocides. A substantial database of environmental and toxicology data has been developed for DMH. These data have been accepted to support the FIFRA registration of a number of halohydantoin active ingredients and biocidal products.

The data adequacy for the HPV/SIDS endpoints for DMH is outlined in the following Table 1. Modeling information and results are included in Appendix A and robust summaries for adequate studies are included in Appendix B.

Table 1: Matrix of Available and Adequate Studies to Fulfill HPV/SIDS Endpoints for DMH

Study Category	IUCLID Sections; HPV/SIDS Endpoints	Adequate Study Available
Physical/Chemical Properties	2.1 Melting Point	√ (M)
	2.2 Boiling Point	M
	2.4 Vapor Pressure	M
	2.5 Partition Coefficient (log P_{ow})	√ (M)
	2.6 Water Solubility	√ (M)
Environmental Fate and Pathways	3.1.1 Photodegradation	√ (M)
	3.1.2 Stability in Water	√
	3.3.2 Transport between Environmental Compartments (Fugacity Model)	M
	3.5 Biodegradation	√
Ecotoxicity	4.1 Acute Toxicity to Fish	√ (M)
	4.2 Acute Toxicity to Aquatic Invertebrates	√
	4.3 Toxicity to Aquatic Plants (e.g. Algae)	See Text
	4.5.1 Chronic Toxicity to Fish	√
	4.5.2 Chronic Toxicity to Aquatic Invertebrates	√
Health Effects	5.1.1 Acute Oral Toxicity	√
	5.1.2 Acute Inhalation Toxicity	√
	5.1.3 Acute Dermal Toxicity	√
	5.4 Repeated Dose Toxicity	√
	5.5 Genetic Toxicity *In Vitro*	√
	5.6 Genetic Toxicity *In Vivo*	√
	5.8 Toxicity to Reproduction	√
	5.9 Developmental Toxicity/Teratogenicity	√
	5.10 Absorption and Elimination	√

√ Denotes an adequate study is available and a robust summary has been prepared (Appendix B)
M – Model data exist (see Appendix A and Appendix B)

<u>Physical/Chemical Properties</u>

Modeling procedures and data are presented in Appendix A; robust summaries for model data are included in Appendix B. A measured melting point value (178 ºC) and a modeled value (150 ºC) fulfill the endpoint requirement. No measured boiling point value was available but the endpoint is of minimal value to understanding the fate and effects of DMH, and the modeled value (367 ºC) is adequate to define the endpoint. The modeled value for vapor pressure (1.36 E-006 mm Hg) indicates that DMH is not volatile. A standard reference text indicates DMH is "soluble in water" (Appendix B); the modeled value (4516 mg/l) also indicates that DMH is soluble in water. Octanol/water partition coefficient (K_{ow}) was experimentally determined (Appendix B). The model prediction for log K_{ow} (-0.27) is consistent with the water solubility and in agreement with the measured value log K_{ow} (0.35). Overall, the measured and model data are adequate to support the physical/chemical properties of DMH for the HPV Chemical Challenge Program, and no additional data development is proposed.

Environmental Fate and Ecotoxicity

Model data for atmospheric degradation (photodegradation) and Level III fugacity (transport and distribution) were available for DMH (Appendix A; robust summaries are included in Appendix B). Aqueous photodegradation, hydrolytic stability, and biodegradation have also been evaluated experimentally (Appendix B). DMH is photolytically stable in aqueous solution and hydrolytically stable. DMH is inherently degradable with adequate acclimation time and slowly degraded without acclimation in the biodegradation studies.

Acute and chronic toxicity of DMH to fish and aquatic invertebrates have been extensively studied (Appendix B). DMH is slightly toxic to fish and aquatic invertebrates with LC_{50} and EC_{50} values ranging from approximately 920 to 14,000 mg/l. The ECOSAR model data for fish toxicity (Appendix A and B) indicate a 96-hour LC_{50} value of 1252 mg/l, which is consistent with the measured values. In addition, chronic toxicity to fish and daphnia has been studied (Appendix B). No studies or model data on the toxicity to aquatic plants are available. The lack of specific data for toxicity to aquatic plants is considered inconsequential to meeting the HPV Chemicals Challenge Program goals since DMH is adequately studied for other species, is relatively harmless to aquatic species, and is primarily used as a manufacturing precursor or found as a degradant of halohydantoin biocides eliciting limited environmental exposure potential with FIFRA registered use applications. Further, the US EPA has registered a number of DMH derivatives as biocides based on the available data, recognizing the limited need for data on the toxicity to aquatic plants. Therefore, no additional data development is proposed.

Human Health-Related Data

Extensive evaluation of the acute toxicity, repeated dose toxicity (including chronic toxicity and carcinogenicity), reproductive and developmental toxicity, and genetic toxicity has been conducted for DMH (Appendix B). These data indicate low toxicity and lack of mutagenic, clastogenic, reproductive or carcinogenic effects for DMH. A single occurrence (4 fetuses in one litter) of adactyly and brachydactyly and an increase in incidence of 27 presacral vertebrae was observed in one rabbit developmental toxicity study. The increase of 27 presacral vertebrae is a common variation found in rabbit developmental toxicity studies. In addition, no effects in development were noted in a rabbit developmental toxicity study conducted with a structurally-related hydantoin, 5,5-ethylmethylhydantoin (EMH), or in two rat developmental toxicity studies conducted with DMH. The human health-related data have been accepted by the EPA for registration of DMH derivatives as biocides. No additional data development is proposed.

Conclusions

Adequate data exist for 5,5-dimethylhydantoin (DMH) to meet the HPV Chemical Challenge Program endpoints. DMH has been extensively studied for potential ecotoxicity and mammalian toxicity. Based on this dataset and the primary use of DMH as a manufacturing precursor and degradant for FIFRA registered halohydantoin biocides with limited human and environmental exposure potentials, no additional data development is proposed.

Appendix A - Modeling Information for DMH

Use of Structure Activity Relationships for DMH

Approaches recommended in the EPA document on the use of structure activity relationship (SAR) in the HPV Chemicals Challenge Program were employed in the assessment of DMH (US EPA, 1999b). Several models were employed to support this review and assessment. The models included several based on structure-activity relationships (SAR), as well as Mackay-type fugacity-based modeling. The SAR models for physical properties were used to estimate melting point, boiling point, vapor pressure octanol-water partition coefficient and water solubility. Other SAR models were used to estimate hydroxyl radical mediated atmospheric photo-oxidation and biodegradation potential. SAR models also were used to obtain conservative estimates of acute toxicity to fish (the model did not provide a value for aquatic invertebrates or plants).

Common Features of the Models

All of the models (except the Mackay-type models) require the input of a molecular structure to perform the calculations. The structure must be entered into the model in the form of a Simplified Molecular Input Line Entry System (SMILES) notation or string. SMILES is a chemical notation system used to represent a molecular structure by a linear string of symbols. The SMILES string allows the program to identify the presence or absence of structural features used by the submodels. The models contain files of structures and SMILES strings for approximately 100,000 compounds, accessible via CAS RNs. SMILES strings cannot be developed for mixtures or chemicals without a single, definable structure.

Estimation of Physical/Chemical Properties

The SAR models for estimating physical properties and abiotic degradation were obtained from Syracuse Research Corporation 2000 (Estimation Programs Interface for Windows, Version 3.10 or EPIWIN v.3.10). The models were used to calculate melting point, boiling point, vapor pressure (submodel MPBPVP), octanol-water partition coefficient (K_{ow}) (submodel KOWWIN) and water solubility (submodel WSKOWWIN). The calculation procedures are described in the program guidance and are adapted from standard procedures based on analysis of key structural features (Meylan and Howard, 1999a, b and c).

Estimation of Environmental Fate Properties

Atmospheric photo-oxidation potential was estimated using the submodel AOPWIN (Meylan and Howard, 2000a). The estimation methods employed by AOPWIN are based on the SAR methods developed by Dr. Roger Atkinson and co-workers (Meylan and Howard, 2000a). The SAR methods rely on structural features of the subject chemical. The model calculates a second-order rate constant with units of cm^3/molecules-sec. Photodegradation based on atmospheric photo-oxidation is in turn based on the rate of reaction (cm^3/molecules-sec) with hydroxyl radicals (HO•), assuming first-order kinetics and an HO• concentration of

1.5 E + 6 molecules/cm^3 and 12 hours of daylight. Pseudo first-order half-lives ($t_{1/2}$) were then calculated as follows: $t_{1/2} = 0.693/[(k_{phot} \times HO\bullet) \times (12\text{-hr}/24\text{-hr})]$.

Estimation of Environmental Distribution

The Level 3 Mackay-type fugacity-based models were obtained from the Trent University's Modeling Center. The specific model used was the generic Equilibrium Concentration model (EQC) Level 3, version 1.01. These models are described in Mackay *et al*. (1996a and b). Fugacity-based modeling is based on the "escaping" tendencies of chemicals from one phase to another. For instance, a Henry's Law constant calculated from water solubility and vapor pressure is used to describe the "escape" of a chemical from water to air or vice versa, as equilibrium between the phases is attained. The key physical properties required as input parameters into the model are melting point, vapor pressure, K_{ow} and water solubility. The model also requires estimates of first-order half-lives in the air, water, soil and sediment. An additional key input parameter is loading of the chemical into the environment.

Estimation of Acute Aquatic Toxicity

Models developed by the US Environmental Protection Agency (EPA) were employed to make estimates of acute toxicity to aquatic organisms, specifically to the fathead minnow (*Pimephales promelas*), a commonly tested fish; a water-column dwelling invertebrate (*Daphnia magna*); and to a commonly tested green alga, *Selenastrum capricornutum*. The models are incorporated in a modeling package called ECOSAR, version 0.99g (US EPA, 2000). ECOSAR may be obtained from the EPA website for the Office of Pollution Prevention and Toxics, Risk Assessment Division. The models calculate inherent toxicity based on structural features and physical properties, mainly the K_{ow} (Meylan and Howard, 1998).

Modeling Information Specific to DMH

The models described above were used for DMH. Estimations of physical/chemical properties (Table A1), environmental fate and distribution, and ecotoxicity (Table A2) were made. The measured physical chemical properties values for melting point (178°C) and octanol-water partition coefficient, log K_{ow} (0.35), were used in the model. Release of DMH to the environment was considered to be 100% to water. The following values were generated from the models:

Table A1: Physical/Chemical Properties Model Data for DMH

Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (mm Hg)	Partition Coefficient (log K_{ow})	Water Solubility (mg/l)
150	366.72	1.36E-06	-0.27	4516

Table A2: Environmental Fate and Ecotoxicity Model Data for DMH*

Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution		Acute Tox. to Fish LC_{50} (mg/l)
k_{phot} = 3.06E-12 $t_{1/2}$ = 3.5 days	Model did not estimate	air: < 0.1% water: 99.8% soil: < <0.01% sediment: 0.2%		1252

* ECOSAR did not provide an estimate of daphnid or algae toxicity

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Meylan, W. and P. H. Howard. 1998. User's Guide for the ECOSAR Class Program, Version 0.99d. Syracuse Research Corporation, North Syracuse, NY.

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